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Stereoselective Conjugate Radical Additions: Application of a Fluorous Oxazolidinone Chiral Auxiliary for Efficient Tin Removal

Jason E. Hein, Jake Zimmerman,[†] Mukund P. Sibi,[†] and Philip G. Hultin*

Department of Chemistry, University of Manitoba, Winnipeg, MB, R3T 2N2 Canada
hultin@cc.umanitoba.ca

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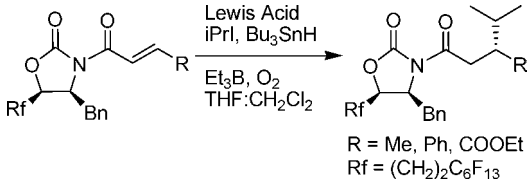
ABSTRACT



A series of asymmetric free-radical-mediated intermolecular conjugate additions using a fluorous oxazolidinone chiral auxiliary has been completed. The fluorous auxiliary facilitated product isolation using fluorous solid phase extractions (FSPE), effectively removing excess organic and organometallic reagents. Parallel reactions carried out with a similar but nonfluorous norephedrine-derived oxazolidinone demonstrated the superior stereoselectivity and purification obtainable with the fluorous chiral auxiliary.

Asymmetric radical reactions have become important tools for synthetic chemists.[1] In many cases, C−C bond formation via radical chemistry can be accomplished using milder conditions than typical ionic reactions, avoiding epimerization and decomposition of sensitive molecules. Stereoselective radical reactions involving acyclic systems, particularly additions to α,β-unsaturated systems, represent valuable transformations, furnishing synthetically useful carbon frameworks.[2]

Asymmetric radical reactions are unquestionably important synthetic tools, and extension of this technology to high-throughput, automated parallel methods would be a great asset. To accomplish this, a supported analogue to the solution phase protocols must be developed. Stereoselective conjugate addition of nucleophilic radicals has been accomplished by applying Lewis acids in conjunction with chiral auxiliaries[3] and chiral catalysts.[4] Asymmetric C−C bond construction using radical chemistry on conventional polymeric supports has been reported;[5] however, the scope of these reactions is limited and no examples of supported stereoselective conjugate addition yet exist.

Although practiced in the laboratory on a routine basis, one of the major drawbacks to tin hydride mediated radical chemistry is the difficulty in removal of the tin byproducts.[6] Several alternatives to tin hydride have been reported in the literature.[7] Curran has demonstrated the utility of a fluorous tin hydride in radical chemistry and noted the ease with

[†] Department of Chemistry, North Dakota State University, Fargo, ND 58105.

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(2) For recent reviews, see: (a) Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051. (b) Zhang, W. *Tetrahedron*, **2001**, *57*, 7237. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.

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(5) (a) Miyabe, H.; Nishimura, A.; Fujishima, Y.; Naito, T. *Tetrahedron* **2003**, *59*, 1901. (b) Ganesan, A.; Sibi, M. P. *Handb. Comb. Chem.* **2002**, *1*, 227−246. (c) Enholm, E. J.; Gallagher, M. E. *Org. Lett.* **2001**, *3*, 3397. (d) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443.

(6) For recent reviews, see: Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. (b) Parsons, A. F. *Chem. Br.* **2002**, *38*, 42. For a recent example of a new method for tin removal, see: Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968 and references therein.

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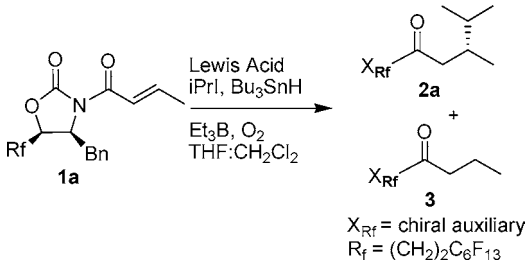
which pure reaction products could be isolated.[8] We surmised that a fluorous chiral auxiliary could provide highly stereoselective radical reactions and optimal purification characteristics. This would allow these reactions to be used in high-throughput and automated parallel methods.

Recently we have demonstrated the utility of a new class of fluorous-supported oxazolidinone chiral auxiliary in titanium-mediated aldol reactions.[9] These compounds are extremely robust and mimic the solution phase performance of the corresponding Evans auxiliaries. Furthermore, products are efficiently and rapidly purified using fluorous solid phase extraction (FSPE). In this communication we report the extension of this technology to asymmetric radical chemistry, demonstrating the first example of a supported stereoselective radical conjugate addition and the complete removal of tin byproducts from the desired product.

Our initial studies were aimed at identifying the most efficient Lewis acid capable of promoting conjugate addition with high stereoselectivity (product **2a**) in preference to direct reduction (product **3**; Table 1). The required crotyl starting material **1a** was prepared using a standard acylation protocol.[10,11] Radical reaction conditions were based on procedures reported by Sibi et al.[12]

Table 1. Effect of Lewis Acid on Radical Conjugate Additions



entry	Lewis acid	yield (%)[b,c]	ratio[d]
1		58	1.1:1
2	$ZrCl_4$	44 (45)	6:1
3	$Fe(ClO_4)_3$	34 (22)	1.2:1
4	$Cu(OTf)_2$	31 (12)	2:1
5	$Sc(OTf)_3$	62 (16)	2:1
6	$Sc(OTf)_3$[e]	82	5:1
7	$La(OTf)_3$	65	1.7:1
8	$Yb(OTf)_3$	88	4:1
9	$Yb(OTf)_3$[e]	91	7.2:1
10	$Pr(OTf)_3$	89	3:1
11	$Dy(OTf)_3$	60 (25)	3:1
12	$Dy(OTf)_3$[e]	79	6:1

[a] Lewis acid (2 equiv), *i*-PrI (10 equiv), Bu_3SnH (5 equiv), Et_3B (10 equiv), O_2, THF/CH_2Cl_2 (1:4), 0 °C, 2 h. [b] Yield based on conversion to **2a** determined by ^1H NMR at 500 MHz. [c] Values in parentheses represent yield of **3** determined by HPLC. [d] Diastereomer ratios were determined by ^1H NMR at 500 MHz. [e] Reaction carried out at −78 °C

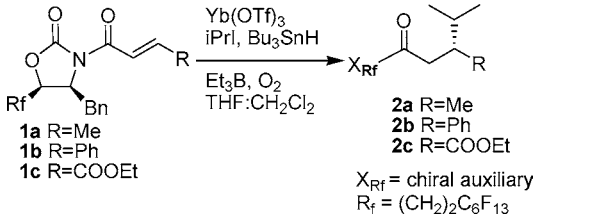
The progress of the reaction was monitored by TLC. On completion the crude reaction material was applied to a silica gel pad, which was washed with hexanes to remove the bulk of the alkyltin species. The products were then liberated with diethyl ether and adsorbed onto FluoroFlash[13] before being applied to an FSPE cartridge.[14] The cartridge was rinsed with 7:3 $MeOH/H_2O$ to remove the organic and organometallic impurities. Subsequent elution with MeOH liberated the products as a mixture of diastereomers. The diastereoselectivity of the reaction was easily determined using ^1H NMR.

This rapid and convenient cleanup protocol allowed us to explore the variation in reaction selectivity with a number of Lewis acids (Table 1). In general, the rare earth Lewis acids (in particular $Yb(OTf)_3$) gave the best results. Good stereoselectivity was observed with a number of Lewis acids, but reduction product **3** was a significant byproduct in some cases (entries 2, 5, 11). This side reaction was suppressed at −78 °C (entry 5 vs 6, 11 vs 12). Reduced temperature afforded significantly better diastereoselectivity (entries 6, 9, 12) in addition to the improved yields.

Sibi et al. have shown that the diastereoselectivity of conjugate radical additions using nonfluorous oxazolidinones depends primarily on the ionic radius of the metal rather than its Lewis acidity.[12,15] This trend appears to be mirrored in our results, as La(III) and Sc(III) both produce similarly poor selectivities, despite their difference in Lewis acidity. Ultimately species such as Yb(III) and Dy(III) display the correct balance of Lewis acidity and ionic size, leading to the highest diastereoselectivity.

We next extended the chemistry to other *N*-acyl fluorous oxazolidinones. The cinnamoyl and monoethyl fumarate derivatives **1b** and **1c** were alkylated under the best conditions from the previous study (Table 2). Products were purified by passage through silica gel followed by FSPE as before, again allowing the diastereoselectivity to be measured with ^1H NMR.

Table 2. Examination of Substrate Variability[a]



entry	product	temp (°C)	yield (%)[b]	ratio[c]
1	**2a**	0	88	4:1
2	**2a**	−78	91	7.2:1
3	**2b**	0	87	2.2:1
4	**2b**	−78	89	4.7:1
5	**2c**	0	93	3:1
6	**2c**	−78	85	6.6:1

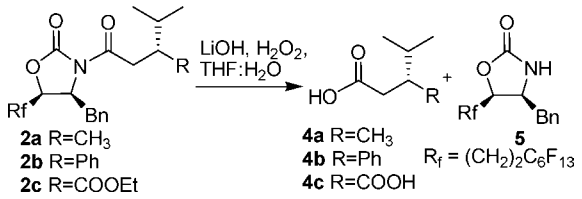
[a] Lewis acid (2 equiv), *i*-PrI (10 equiv), Bu_3SnH (5 equiv), Et_3B (10 equiv), O_2, THF/CH_2Cl_2 (1:4). [b] Isolated yield. [c] Diastereomer ratios were determined by ^1H NMR at 500 MHz.

(7) Selected examples: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. (b) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071. (c) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726. (d). Cho, D. H.; Jang, D. O. *Bull. Kor. Chem. Soc.* **2003**, *24*, 15. (e) Khan T. A.; Tripoli R.; Crawford J. J.; Martin C. G.; Murphy J. A. *Org. Lett.* **2003**, *5*, 2971.

As in the reactions of crotyl derivative **1a**, performing the reactions of **1b** and **1c** at −78 °C significantly improved the diastereoselectivity. Furthermore, acceptable levels of selectivity were obtainable even at 0 °C using our fluorous oxazolidinone, in contrast to the Evans auxiliary with which cryogenic conditions were necessary.[16]

The diastereomers of the conjugate addition products **2a**−**c** were separated using HPLC. In each case, the new stereocenter in the major diastereomer had the *R* configuration. This was determined by hydrolysis of the addition products **2a**−**c** to give the known carboxylic acids **4a**−**c**[17] (Scheme 1). The observed stereochemistry represents radical addition

Scheme 1

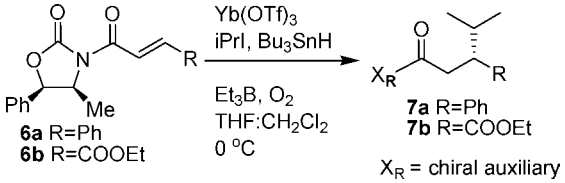


from the less hindered face of the alkene, which is consistent with the behavior of other oxazolididone chiral auxiliaries under similar conditions. [3a,12]

Following FSPE cleanup of the products, no further purification was necessary, even when a large excess (5 equiv) of tributyltin hydride was present. This was encouraging, as alkyltin species are typically very difficult to remove from reaction products. Curran et al. have shown that fluorous alkyltin compounds are effectively removed from organic materials by fluorous liquid−liquid extraction.[8a] This method provides a complementary technique to the work previously reported by Curran, allowing the selective extraction of reaction products, as opposed to capture of undesirable reagents.

The effectiveness of the FSPE technique was evaluated quantitatively by measuring the residual tin content of the crude reaction products obtained from both fluorous and nonfluorous chiral auxiliaries. The oxazolidinone derived from norephedrine[18] was selected as the nonfluorous candidate, as a result of its similar *syn*-4,5 substitution pattern. The *N*-cinnamoyl and *N*-monoethyl fumarate derivatives **6a** and **6b** were synthesized and alkylated at 0 °C under the same conditions employed for the fluorous oxazolidinones **1a**−**c** (Table 3).

Table 3. Radical Conjugate Addition Using Norephedrine Derivatives[a]



entry	compound	yield (%)[b]	ratio[c]
1	**7a**	82	1.7:1
2	**7b**	87	1.3:1

[a] Lewis acid (2 equiv), *i*-PrI (10 equiv), Bu_3SnH (5 equiv), Et_3B (10 equiv), O_2, THF/CH_2Cl_2 (1:4), 0 °C, 2 h. [b] Isolated yield. [c] Diastereomer ratios were determined by ^1H NMR at 500 MHz.

Both fluorous and norephedrine compounds were purified using the combination of silica and fluorous solid phase extractions described above. The total tin content was measured after each stage using atomic absorption spectroscopy (Table 4).

Table 4. Residual Tin in Samples[a]

entry	compound	silica pad (% w/w)	FSPE (% w/w)	flash column (% w/w)
1	**2a**	3.7	0.054	
2	**2b**	6.4	0.070	
3	**7a**	6.6	6.6[b]	0.013
4	**7b**	4.5	4.5[b]	0.023

[a] Determined by atomic absorption spectroscopy. [b] Material was not retained on FSPE cartridge and isolated in 7:3 MeOH/H_2O wash.

The first stage using standard silica gel gave similar results for all compounds, leaving behind between 3.7% and 6.6% tin by weight. The products of this process were then subjected to FSPE. Table 4 shows that FSPE is very effective at removing alkyltin species from fluorous materials, while nonfluorous substances coeluted with the alkyltin compounds. It is also evident that the fluorous solid phase is not sequestering alkyltin species (entries 1, 2 vs 3, 4). To remove the excess tin from the norephedrine derivatives, a third flash chromatography step was required. The FSPE purification

(8) (a) Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607. (b) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. (c) Crombie, A.; Kim, S.-Y.; Hadida, S.; Curran, D. P. *Org. Synth.* **2003**, *79*, 1.

(9) Hein, J. E.; Hultin, P. G. *Synlett* **2003**, 635.

(10) Soloshonok, V. A.; Ueki, H.; Jiang, C.; Cai, C.; Hruby, V. J. *Helv. Chim. Acta* **2002**, *85*, 3616.

(11) Fluorous oxazolidinone **5** was synthesised from L-phenylalanine using a modification of a procedure previously reported. See ref 9 for details.

(12) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517.

(13) FluoroFlash silica gel was obtained from Fluorous Technologies, Inc. and has a perfluorooctylethylsilyl ($C_8F_{17}CH_2CH_2Si$) bonded phase.

(14) For details, see Supporting Information.

(15) Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, *4*, 2929.

(16) Isopropyl radical addition to crotonate derived from 4-benzyloxazolidin-2-one using ytterbium triflate as a Lewis acid proceeds with 2:1 diastereoselectivity. See ref 12 for details.

(17) Absolute configuration determined by chemical correlation to literature results. **4a**, (*R*)-3,4-Dimethylpentanoic acid: Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235. **4b**, (*R*)-3-Phenyl-4-methylpentanoic acid: Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. **4c**, (*R*)-2-isopropylsuccinic acid: Lawston, I. W.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2629.

(18) The oxazolidinone was synthesized from (−)-(1*R*,2*S*)-norephedrine using triphosgene by adapting the reported procedure by Sibi et al. See: Sibi, M. P.; Rutherford, D.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc.* **1999**, *121*, 7509. See Supporting Information section for details.

was faster than standard chromatographic methods, did not require tedious fraction collection, and used far less solvent to obtain a comparable removal of tin.

In conclusion, we have demonstrated that the fluorous chiral auxiliary is an effective tool for stereoselective radical chemistry, offering good stereocontrol and superior purification properties. Following the radical addition, FPSE yields products free of organometallic impurities, which could be immediately applied in further chemistry. Ultimately, this will assist the application of radical chemistry in high-throughput, automated synthesis.

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Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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